

REMARKS

1. The Invention

The invention of the above-identified application is directed to cryopreserved hematopoietic stem and other blood cells, e.g. progenitor cells, from neonatal or fetal blood. Neonatal blood may be obtained from the umbilical cord. The cryopreserved fetal or neonatal stem and other blood cells of the present invention, upon thawing, may be used for hematopoietic reconstitution in patients with various diseases and disorders such as anemias, malignancies, autoimmune disorders, and other immune dysfunctional deficiencies. Alternatively, fetal or neonatal hematopoietic stem, and other blood cells, e.g. progenitor cells, which contain a heterologous gene sequence can be used for hematopoietic reconstitution in gene therapy.

The Examples set forth in the specification demonstrate the presence of hematopoietic stem and progenitor cells in collected human umbilical cord blood and the cryopreservation of cord blood stem and progenitor cells. Moreover, the studies described in the Broxmeyer Declaration, submitted herewith, demonstrate that hematopoietic reconstitution of a patient by infusion of HLA compatible allogeneic umbilical cord blood stem and progenitor cells can be achieved for treatment of Fanconi's anemia.

2. The Examiner's Rejections of the Claims Under 35 U.S.C. §112

Claims 1-9 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The bases for the Examiner's rejection is two-fold. Firstly, the Examiner contends that the specification fails to disclose the claimed composition. Secondly, the Examiner contends that the

specification fails to disclose specific compositions wherein the components of the claimed mixture are put to use. These rejections are in error and should be withdrawn for reasons discussed in detail below.

2.1. The Claimed Compositions Are Adequately Disclosed in the Instant Specification

Firstly, the Applicants assert that the cryopreserved hematopoietic human stem and other blood cells (e.g. progenitor cells) obtained from human cord blood or fetal blood are adequately disclosed in the specification. The Applicants invite the Examiner's attention to Section 5.1, pp. 24-26 of the specification, which teaches the isolation from blood of fetal or neonatal hematopoietic stem and progenitor cells. Section 5.1.3.1, pp. 36-42, specifically teaches the physical and/or immunological separation of neonatal blood cells to enrich for hematopoietic stem and progenitor cells, and Section 5.1.3.2 teaches methods for culturing in vitro hematopoietic stem and progenitor cells. Assays for hematopoietic stem and progenitor cells are disclosed in Section 5.4.2, pp. 49-50. Table V, pp. 94-95 shows a comparison of the number of progenitor cells present in human umbilical cord blood before and after freeze-thawing. Furthermore, the examples Section 6.2, and Table III disclose the presence of various hematopoietic progenitor cells in neonatal human blood, both before and after cryopreservation. It is clear that cryopreserved human neonatal and fetal blood contains stem and other cells such as progenitor cells.

In addition, the Applicants contend that human umbilical cord/fetal blood was known in the art to contain hematopoietic stem and progenitor cells at the time of filing

the above-identified application. A patent need not disclose what is well known in the art. In re Wands, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). Skill in the art can be used to supplement what is disclosed; a patent need not specify details which are not part of the invention and which a person skilled in the art would understand. Rengo Co. Ltd. v. Mollins Machine Co., Inc., 211 U.S.P.Q. 303, 319 (3d Cir. 1981). The Applicants invite the Examiner's attention to the articles listed below that were available to one of ordinary skill in the art as of the filing date of the above-identified application. The Applicants have arranged the articles in groups of related subject matter.

(a) The following articles disclose the presence of stem cells in human umbilical cord blood.

- (1) Knudtzon, In vitro growth of granulocytic colonies from circulating cells in human cord blood, Blood 43:357-361 (1974) (reference AA of record).
- (2) Prindull et al., Hematopoietic stem cells (CFU) in human cord blood, Acta Paediatr. Scand. 67:413-416 (1978) (reference AB of record).

(b) The following articles disclose the presence of circulating hematopoietic progenitor cells in human fetal blood and in cord blood.

- (1) Vainchenker et al., Growth of human megakaryocyte colonies in culture from fetal, neonatal, and adult peripheral blood cells: Ultrastructural analysis, Blood Cells 5:25-42 (1979) (reference AE of record).
- (2) Linch et al., Studies of circulating hematopoietic progenitor cells in human fetal blood, Blood 59:976-979 (1982) (reference AH of record).
- (3) Nakahata and Ogawa, Hematopoietic colony-forming cells in umbilical cord blood with extensive capability to generate mono- and multipotential hematopoietic progenitors, J. Clin. Invest. 70:1324-1328 (1982) (reference AG of record).

The Applicants wish to point out to the Examiner that Linch et al. also suggests the presence of stem cells in human fetal blood (p. 978, col. 1).

Furthermore, Applicants' specification discloses cryopreserved compositions of human neonatal or fetal blood containing stem and other blood cells such as progenitor cells. The Examiner's attention is directed to p. 20, lines 12-14 ("hematopoietic stem and progenitor cells of neonatal or fetal blood, that are cryopreserved"), to Section 5.2, pp. 43-46 (describing cryopreservatives), and to the example sections, in particular Section 6.4, pp. 79-80 (describing the mixture of human cord blood stem and progenitor and other blood cells with cryoprotective (a cryopreservative) medium).

In view of the disclosures of the instant specification of cryopreserved compositions of human neonatal and fetal blood, which blood is shown by Applicants and is known in the art to contain stem and progenitor cells, Applicants submit that the instant specification adequately discloses the claimed compositions and is therefore enabling with respect to such compositions.

2.2. The Uses of the Claimed Compositions are Clearly Disclosed by the Instant Specification

Applicants contend that the uses for the claimed compositions are clearly disclosed in the specification. The Applicants would like to draw the Examiner's attention to Section 5.6, pp. 50-64 of the specification, which discloses in detail the various therapeutic uses of the claimed compositions. "Reconstitution of the hematopoietic system (or immune system) with the neonatal stem and progenitor cells of the present invention can be therapeutically valuable for a large number of diseases and disorders"

(instant specification at p. 50, lines 24-27). Such diseases and disorders include but are not limited to those resulting from dysfunction of normal blood cell production and maturation, hematopoietic organ malignancies, malignant solid tumors of non-hematopoietic origin, and autoimmune conditions (see instant specification at p. 51, line 15 through p. 64, line 32).

In addition, the Examiner's attention is directed to p. 96, line 23 to p. 97, line 1 of the specification:

By standardizing published data by patient weight, and assuming a patient weight of 150 pounds (67.5 kilograms), the calculated number of CFU-GM needed for successful hematopoietic reconstitution using autologous bone marrow cells ranges from $2-425 \times 10^4$, with faster recovery noted using greater than 10×10^4 CFU-GM.

The data presented in Table III, *supra*, for 81 cord blood collections, analyzed for day 14 CFU-GM count, shows a range of $0-109 \times 10^4$ CFU-GM per Ficoll-Hypaque-separated individual blood collections. Seventy samples contained greater than or equal to 2×10^4 CFU-GM, while thirty samples contained greater than or equal to 10×10^4 CFU-GM.

Therefore, sufficient quantities of neonatal/fetal progenitor cells can be obtained to carry out hematopoietic reconstitution.

Moreover, the Applicants would like to direct the Examiner's attention to the Broxmeyer Declaration under Rule 132. Evidence is presented in the Broxmeyer Declaration which demonstrates that hematopoietic reconstitution for the treatment of Fanconi's anemia can be achieved by infusion of compositions containing the cryopreservative DMSO (10% (v/v)) and human neonatal cord blood containing stem and progenitor cells. Specifically, the Broxmeyer Declaration describes the successful reconstitution of a 5 year old boy afflicted with

Fanconi's anemia, by infusion of the cord blood of an HLA compatible healthy sibling donor. Complete engraftment of the patient's myeloid system with donor cells was achieved.

The Applicants contend that the instant specification's description of the claimed compositions and their uses, as well as the evidence presented in the Broxmeyer Declaration of the use of the claimed compositions to effect hematopoietic reconstitution for the treatment of Fanconi's anemia, would enable one of ordinary skill in the art to identify and utilize the claimed compositions according to the instant invention.

The disclosure is thus enabling, and Applicants respectfully request that the Examiner's rejection under 35 U.S.C. §112 be withdrawn.

3. The Examiner's Rejections of
the Claims Under 35 U.S.C. §103

The Examiner has rejected claims 1-9 under 35 U.S.C. §103 as being obvious over Nothdurft et al., Sarpel et al., Korbling et al., or Castaigne et al. The Examiner states that each reference teaches the cryopreservation with cryoprotectant of combinations of hematopoietic stem cells, which is so proximate to the claimed invention as to render the claims prima facie obvious.

The objective standard for obviousness under 35 U.S.C. § 103 as set forth clearly by the Supreme Court of the United States in Graham v. John Deere, Inc., 383 U.S. 1 (1966) requires the Examiner to ascertain: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the differences between the claimed subject matter and the prior art. 383 U.S. 1, 17 (1966). The obviousness or nonobviousness of the claimed subject matter

must be determined in light of these inquiries. Moreover, the Graham Court also explained that secondary considerations such as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized in determining the obviousness or nonobviousness of the invention.

Following Graham, the Court of Customs and Patent Appeals (CCPA) and its present successor, the Court of Appeals for the Federal Circuit (CAFC), have held the following considerations to be objective evidence of nonobviousness; long felt need, commercial success, failure of others, copying and unexpected results. In re Sernaker, 217 U.S.P.Q. 1 (Fed. Cir. 1983); In re Imperato, 179 U.S.P.Q. 710 (C.C.P.A. 1973). In fact, the CAFC has consistently made clear that when evidence of such secondary considerations is present, it must be considered by the Examiner or a court in determining a question of obviousness. See e.g. Ashland Oil v. Delta Resins & Refractories Inc., 237 U.S.P.Q. 785 (Fed. Cir. 1984); Stratoflex Inc. v. Aeroquip Corp., 238 U.S.P.Q. 871 (Fed. Cir. 1983).

The proper application of the Graham test for obviousness, as clarified by the CAFC, leads to the inescapable conclusion that the claimed compositions could not possibly have been obvious in view of the cited references. In sum, applying the proper standard for determining obviousness, the cited references do not render the claimed invention obvious because: (a) none of the cited references disclose or suggest hematopoietic reconstitution by use of human neonatal or fetal cells; (b) the Examiner has failed to evaluate the secondary considerations which are indicia of nonobviousness; and (c) the Examiner's rejection involves the improper use of hindsight gained from the Applicants' specification.

3.1. The References Cited By The Examiner
Neither Disclose Nor Suggest the Use of
Neonatal or Fetal Cells for Hematopoietic
Reconstitution

As described supra, the Examiner has contended that the claims are obvious over Nothdurft et al., Sarpel et al., Korbling et al., or Castaigne et al., since each of the references teach the cryopreservation of combinations of hematopoietic stem cells. The Examiner concludes that this teaching is so proximate to the claimed invention as to render the claims prima facie obvious.

Applicants respectfully disagree, and point out that there is no suggestion or observation in Northdurft et al., Sarpel et al., Korbling et al., or Castaigne et al. of the use of cryopreserved hematopoietic stem or progenitor cells from human fetal or umbilical cord blood. Nothdurft et al. and Sarpel et al. report studies on hematopoietic reconstitution in dogs. Nothdurft et al. discloses cryopreserved mononuclear cells derived from the peripheral blood of dogs, neither neonatal nor fetal, as a source of stem cells for autologous hematopoietic reconstitution. Sarpel et al. describes the collection, characterization, and the transfusion of cryopreserved mononuclear cells derived from the peripheral blood of dogs, neither neonatal nor fetal, for autologous hematopoietic reconstitution. No suggestion is made in these references of the use of cryopreserved hematopoietic stem cells and other blood cells from human fetal or cord blood.

Korbling et al. and Castaigne et al. disclose the use of cells derived from adult human peripheral blood for hematopoietic reconstitution. Korbling et al. describes the hematopoietic reconstitution of a patient with Burkitt's lymphoma using autologous cryopreserved peripheral blood

mononuclear cells. Castaigne et al. describes the hematopoietic reconstitution of a patient with promyelocytic leukemia using autologous peripheral blood mononuclear cells collected from the adult patient and cryopreserved. Again, neither of the above references suggest or teach the use of cryopreserved hematopoietic stem cells and other blood cells from human fetal or cord blood.

In determining whether a case of prima facie obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification. In re Lalu, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). The Patent and Trademark Office (PTO) must weigh the entire body of evidence, that arising in the prior art and that provided by the Applicants when passing on obviousness. In re Margolis, 228 U.S.P.Q. 940 (Fed. Cir. 1986). A PTO rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination to suggest the desirability of the claimed subject matter.

The Applicants assert that the references cited by the Examiner at most teach the use of cryopreserved hematopoietic stem cells and other blood cells from non-neonatal/fetal donor peripheral blood for hematopoietic reconstitution. In contrast, the above-identified application teaches compositions containing hematopoietic stem cells and other blood cells, from human fetal or umbilical cord blood, and a cryopreservative. The use of human neonatal/fetal blood cells is nonobvious. As pointed out in the specification on p. 23, neonatal blood obtained from the umbilical cord and placenta is customarily discarded at birth! Such neonatal/fetal blood was deemed in the prior

art to be so lacking in utility that it was routinely discarded. It was not until Applicants' invention that the utility of such blood cells, in combination with a cryopreservative, was recognized. Therefore, the teachings of the cited references could not have suggested to one of ordinary skill in the art the claimed compositions, nor their uses in hematopoietic reconstitution.

3.2. The Examiner Has Failed To Evaluate
The Secondary Considerations Which Are
Indicia of Nonobviousness

As discussed supra, the following considerations are objective evidence of nonobviousness: long felt need, commercial success, failure of other, copying, and unexpected results. E.g., In re Sernaker, 227 U.S.P.Q. 1 (Fed. Cir. 1983); In re Imperata, 179 U.S.P.Q. 730 (C.C.P.A. 1973). It is well established case law that evidence of the satisfaction of a long recognized need and difficulties encountered by those skilled in the art, are classical indicia of nonobviousness. In re Dow Chemical Co., 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988); Under Sea Industries Inc. v. Decor Corp., 4 U.S.P.Q. 2d 1772 (Fed. Cir. 1987); and Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986). The Applicants contend that the long felt need for effective, safely and easily obtainable compositions for use in hematopoietic reconstitution, and the difficulties encountered with compositions disclosed in the prior art for use in hematopoietic reconstitution, provide further proof of nonobviousness of the instant invention.

As discussed in Section 2 of the instant specification, some years prior to the filing of the above-identified application, there existed recognition in the art that successful hematopoietic reconstitution would be

valuable in the treatment or prevention of various diseases and disorders such as anemia, malignancies, autoimmune disorders, and other immune dysfunctions and deficiencies.

As summarized in Section 2.2, pp. 9-12 of the instant specification, bone marrow, adult peripheral blood (disclosed in Nothdurft et al., Sarpel et al., Korbling et al. and Castaigne et al.), fetal liver, neonatal spleen, and neonatal thymus have been investigated as possible sources of stem cells and other blood cells for hematopoietic reconstitution. Bone marrow transplantation has been used in attempts to treat various fatal or crippling diseases including aplastic anemia, Fanconi's anemia, immune deficiencies, cancers such as lymphomas or leukemias, carcinomas, various solid tumors, genetic disorders of hematopoiesis, treatment of inherited storage diseases, sickle cell disease, and osteoporosis. Peripheral blood cells have been used in attempts to treat various leukemias.

However, there are a number of drawbacks to each of the prior art systems that had been investigated as possible sources of stem cells and other blood cells for hematopoietic reconstitution at the time of filing the above-identified application. With respect to bone marrow, as stated on p. 25, lines 13-15 of the specification, bone marrow collection is an invasive procedure, thus posing some risk to the donor, and is expensive and laborious: "[A]t present, the collection of bone marrow cells for transplantation is a traumatic experience which is costly in terms of time and money spent for hospitalization." Furthermore, with respect to attempted autologous hematopoietic reconstitution, bone marrow transplantation entails many disadvantages not

encountered with use of neonatal cells, including the sick or suboptimal condition of the donor. As stated on p. 10, line 23 thru p. 11, line 15 of the instant specification:

Present use of bone marrow transplantation is severely restricted....Even in such an autologous system, the danger due to undetectable contamination with malignant cells, and the necessity of having a patient healthy enough to undergo marrow procurement, present serious limitations. [references omitted]

In contrast, in the use of neonatal or fetal cells as provided by the present invention, neonatal blood that is otherwise discarded is readily obtainable for use without risk to the donor.

The Examiner's attention is further directed to the following description of additional long-desired advantages supplied by the use of human neonatal/fetal blood cells:

Furthermore, the prospects of success in bone marrow transplantation decline with age; although it is not clear whether the age of donor or patient is more important, it is proper to infer that younger (neonatal) cells are preferable for hematopoietic reconstitution. Such neonatal or fetal cells have not been subjected to the "environmental outrage" that adult cells have undergone. Also, as an example of novel medical applications which may be feasible with neonatal cells but not with conventional bone marrow transplantation, restoration with self cells taken at birth can be valuable in the treatment of disorders such as declining immune responsiveness and autoimmunity (immune reactions against one's own tissues) which occur in increasing frequency with age.

...
There are additional reasons for preferring the use of neonatal cells for hematopoietic reconstitution as provided by the present invention. Neonatal blood is a preferred source of cells for hematopoietic reconstitution, since it is free from viral and microbial agents, known or unknown, latent or otherwise, that may be encountered in later life, other than those transmitted from the mother or during labor and delivery. In addition, in view of the extent to which the hematopoietic stem cell may possibly share with other cells the limitation in total number of cell divisions that it may undergo before senescence, it is proper to assume that the neonatal hematopoietic stem cell has a self-renewal and reconstituting capacity that

is at least as great, and perhaps greater, than that of hematopoietic stem cells obtained at any later time in life.

In adults, stem and progenitor cells are mostly confined to the bone marrow; very few circulate in the blood. In the newborn human or animal, however, stem and progenitor cells circulate in the blood in numbers similar to those found in adult bone marrow. Doubtless this reflects the great demands for blood formation of the growing infant. We calculate that the restorative capacity of neonatal blood contained in the human umbilical cord and placenta, which are customarily discarded at birth, equals or exceeds that of the average donation of an adult's bone marrow. (instant specification at p. 22, lines 5-18, and p. 23, lines 3-27).

With respect to the use of adult peripheral blood cells, it appears that while in some studies promising results have been obtained for patients with various leukemias and with lymphoma, other studies using peripheral blood have failed to effect reconstitution. For example, Hersko et al., 1979, the Lancet 1.:945-947 (reference AT of record), discloses the failure to effect hematopoietic reconstitution using adult peripheral blood mononuclear cells in a patient suffering from aplastic anemia. Additionally, the collection of peripheral blood can be time consuming and uncomfortable. Furthermore:

Many of the relative disadvantages discussed supra of the use of bone marrow cells for hematopoietic reconstitution [disadvantages due to age], also apply to the use of adult peripheral blood for such reconstitution, and thus, the use of neonatal cells for hematopoietic reconstitution according to the present invention provides distinct advantages over the employment of adult peripheral blood. (instant specification at p. 22, lines 19-25)

There are also numerous difficulties in using blood obtained from fetal liver, neonatal spleen, and fetal and neonatal thymus. Firstly, only limited success has been obtained in studies using fetal liver or fetal thymus transplants. Reconstitution was not observed by Ochs et al.,

1981, Pediatr. Res. 15 (4 part 2):601 (reference BH of record), who disclose the failure of fetal liver cells to effect the immune reconstitution of patients with severe combined immunodeficiency associated with adenosine deaminase deficiency. Touraine et al., 1983, Birth Defects 19(3):139-142 (reference BL of record), disclose results from a study of fetal liver transplantation in which B-cell reconstitution was observed in only 11 out of 23 patients and T-cell reconstitution was observed in only 7 out of 23 patients. It was speculated that the gender of the fetus, and fetal age, were determining factors in the success of the hematopoietic reconstitution. The Applicants would also further like to point out to the Examiner the difficulty in obtaining fetal liver or other organ samples.

In contrast, the compositions of the present invention supply a long-felt need for useful, safely and easily obtainable sources of hematopoietic stem and other cells useful for hematopoietic reconstitution. The neonatal/fetal blood cells can easily be obtained from umbilical cord blood available on delivery of the donor baby. Specifically, cord blood can be obtained by direct drainage from the cord and/or by needle aspirations from the delivered placenta at the root and at distended veins. Therefore, cord blood can be obtained without trauma to the donor, easily and inexpensively. The Applicants would like to further point out that many difficulties had been experienced in obtaining hematopoietic reconstitution using methods known in the prior art. In contrast, as disclosed in the accompanying Broxmeyer Declaration, the compositions of the present invention have been used to carry out the successful reconstitution of the hematopoietic system, in a patient with Fanconi's anemia.

The Applicants conclude that the claimed compositions fulfill a long felt need for an easily accessible source for stem and other blood cells that can be used for hematopoietic reconstitution in patients with various diseases and disorders. Consideration of the secondary criteria for nonobvious clearly evidences the nonobviousness of the instant invention.

3.3. The Examiner's Rejection Involves the
Improper Use of Hindsight Gained
From the Applicants' Specification

The Applicants believe that the Examiner's use of the cited references to reject the claims as obvious under 35 U.S.C. §103, indicates the improper use of hindsight gained from the Applicants' specification. Hindsight should be avoided in applying the nonobviousness requirement. Panduit Corp. v. Dennison Mfg. Co., 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987). One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. In re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Without the benefit of hindsight, the teachings of the references cited by the Examiner, alone or in combination, could not possibly render obvious the claimed compositions. As discussed supra, umbilical cord blood was routinely discarded. Therefore, the claimed composition of neonatal/fetal hematopoietic stem cells and other blood cells and a cryopreservative could not have been foreseen by a person of ordinary skill in the art at the time of the filing of the above-identified patent application. The Examiner's finding of obviousness could only have been arrived at through the prohibited use of the instant claims "as a frame, and individual noted parts of separate prior art references

as a mosaic to recreate a facsimile of the claimed invention." Gore & Associates, Inc. v. Garlock, Inc., 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 105 S.Ct. 1972 (1984).

In view of the foregoing discussions, the Applicants assert that the claimed invention is not obvious over Nothdurft et al., Sarpel et al., Korbel et al., or Castaigne et al. Therefore, the Applicants respectfully request that the Examiner's rejection of the claims under 35 U.S.C. §103 be withdrawn.

4. Conclusion

The Applicants respectfully request the entry of the foregoing remarks into the file of the above-captioned application. The Applicants believe that each ground for rejection or objection has been successfully overcome or obviated and that the claims are in condition for allowance. An early allowance of the pending claims is earnestly requested.

Respectfully submitted,
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